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- (s) Penetration enhancement with binary system of cell envelope disordering compounds and lower alcohols.
- Penetration-enhancing pharmaceutical compositions for topical transepidermal and percutaneous application are disclosed. These compositions are made up of a safe and effective amount of an active pharmaceutical permeant contained in a novel penetration-enhancing vehicle comprising, (i) a cell-envelope disordering compound; and (ii) a lower alkanol selected from the group consisting of ethanol, propanol and isopropanol and mixtures thereof. The weight ratio of cell-envelope disordering compound to lower alkanol is between about 50:1 to 1:50 and preferably between about 9:1 and 1:9. Preferred cell-envelope disordering compounds are oleic acid, oleyl alcohol, glycerol oleates, methyl oleate, methyl laurate and mixtures thereof. The novel penetration enhancer vehicles are non-irritating to the skin and enhance the penetration of a broad spectrum of pharmaceutical permeants including hydrophilic salts.

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PENETRATION ENHANCEMENT WITH BINARY SYSTEM OF CELL ENVELOPE DISORDERING COMPOUNDS AND LOWER ALCOHOLS

This invention relates to compositions which enhance the penetration of pharmaceutically-active agents through the integument. More particularly, this invention relates to binary combinations of penetration enhancers which facilitate percutaneous and transepidermal delivery of a broad range of pharmaceutically-active agents.

The resistance of the skin to being penetrated by pharmaceutically-active agents is well documented. As compared to mucosal tissues, the stratum corneum is compact and highly keratinized. The lipids and proteins of the stratum corneum, although relatively thin, is compact and quite impermeable. Such impermeability of the skin is highly essential to the well being of a living organism in that it serves as a barrier to the ingress of pathogens and toxic materials, and the egress of physiologic fluids.

The impermeability of pharmaceutical agents through the skin is due to the nature of the very thin stratum corneum layer which is only 10-15 cells, i.e. about 10 microns thick. This layer is formed naturally by cells migrating toward the skin surface from the basal layer. Cells slowly move from the basal layer to the surface where they are sloughed off. As they progress toward the surface they become progessively more dehydrated and keratinized.

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Because of the advantages of dermal application of pharmaceutically-active agents, various penetration enhancers have been sought. A penetration enhancer is one or more compounds which alter the skin as a barrier to increase the flux of a desired pharmaceutical permeant across the skin.

Penetration enhancers have been primarily categorized according to their ability to enhance permeant flux via three pathways. The first is the continuous polar or aqueous pathway composed of proteins. It is though that solvent swelling or protein conformational changes provide the key to altering the penetration of the polar pathway. Surfactants alter the transport of polar permeant molecules to a much greater extent than the transport of nonpolar permeants. Solvents such as DMSO, 2-pyrrolidone and dimethylformamide can swell the stratum corneum to also enhance the polar pathway.

The second pathway is a continuous non-polar pathway consisting of lipids. The key to altering this pathway appears to be fluidizing the lipids which, in the stratum corneum, appear to be crystalline. Solvents such as DMSO, 2-pyrrolidone, and dimethylformamide, previously mentioned also appear able to solubilize or fluidize lipids. Other solvents include diols such as glycerol and propylene glycol.

The third pathway is a heterogeneous polar-nonpolar multilaminate of lipids and proteins. Binary vehicles appear best suited to act as enhancers on this multilaminate pathway. Prior art binary systems consist of a particular category of a polar solvent combined with a variety of compounds generally referred to as "cell-envelope disordering compounds".

U. S. Patent 4,537,776, Cooper, issued August 27, 1985 contains an excellent summary of prior art and background information detailing the use of certain binary systems for permeant enhancement. Because of the completeness of that disclosure, the information and terminology utilized therein are incorporated herein by reference. That patent teaches using a binary system wherein N-(2-hydroxyethyl)pyrrolidone is used as the solvent and the cell-envelope disordering compounds are selected from the group consisting of methyl laurate, oleic acid, oleyl alcohol, moloolein, myristyl alcohol and mixtures thereof.

Similarly, European Patent Application 43,739, published January 13. 1982, teaches using selected diols as solvents along with a broad category of cell-envelope disordering compounds for delivery of lipophilic pharmacologically-active compounds. This reference also teaches that cosmetically acceptable solvents may also be combined with permeant and the diol and cell-envelope disording compounds provided the solvent evaporates rapidly and completely to leave only the active components of the composition at the site of application. The acceptable solvents are stated to be ethanol or isopropanol. Because of the detail in disclosing the cell-envelope disordering compounds and the diols, the disclosure of European Patent Application 43,738 is also incorporated herein by reference.

Most of the cell-envelope disordering compounds mentioned in these publications are unsaturated lipid components having polar head groups.

A binary system for enhancing metoclopramide penetration is disclosed in UK Patent Application GB 2,153,223 A, published August 21, 1986 and consists of a monovalent alcohol ester of a C8-32 aliphatic monocarboxylic acid (unsaturated and/or branched if C18-32) or a C6-24 aliphatic monoalcohol (unsaturated and/or branched if C14-24) and an N-cyclic compound such as 2-pyrrolidone, N-methylpyrrolidone and the like. It is postulated that the N-cyclic compound serves a solvent function which carries the active agent whereas the esters or alcohols serve as adjuvants to open up the stratum corneum, i.e. as cell-envelope disordering compounds.